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Poor Outcome with Nonmyeloablative Conditioning Regimen before Cord Blood Transplantation for Patients with High-Risk Acute Myeloid Leukemia Compared with Matched Related or Unrelated Donor Transplantation

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A B S T R A C T

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is recommended for patients with high-risk acute myeloid leukemia (AML). In many situations, a matched related (MRD) or matched unrelated donor (MUD) is lacking, in which case unrelated cord blood units (UCB) provide an alternative. We analyzed the outcome of consecutive high-risk AML patients prepared with reduced-intensity conditioning (RIC) regimens and allografted with UCB (n = 32) and compared their outcome with high-risk AML patients who underwent transplantation with MRD/MUD (n = 49) in the same period of time. Grade III to IV acute graft-versus-host disease (GVHD) occurred slightly more frequently in the UCB group (25%) than in the MRD/MUD group (8%) ($P = .069$). Conversely, we found a lower incidence of extensive chronic GVHD in the UCB group (6%) than in the MRD/MUD group (20%, $P = .085$). Nonrelapse mortality at 4 years was 16% and 22% in the UCB and MRD/MUD groups, respectively ($P = .529$). The cumulative incidence of relapse at 4 years was significantly higher in the UCB group (60%) than in the MRD/MUD group (27%, $P = .006$). Leukemia-free survival (LFS) and overall survival (OS) at 4 years were 25% and 34%, respectively, in the UCB group and 50% and 56%, respectively, in the MRD/MUD group (LFS, $P = .029$; OS, $P = .072$). Multivariate analyses adjusted by cytogenetics and disease status at the time of Allo-HSCT revealed that use of UCB remained an independent predictive factor of shorter LFS (hazard ratio, 2.0; 95% confidence interval, 1.1 to 3.6; $P = .018$), and was associated with a trend for shorter OS (hazard ratio, 1.7; 95% confidence interval, .9 to 3.2; $P = .093$). Whereas UCB provides an alternative for patients with high-risk AML lacking an MRD/MUD, the high incidence of relapse after RIC-based UCB Allo-HSCT is a concern. Attempts to improve leukemic control with UCB Allo-HSCT are warranted, as well as the evaluation of other alternative donors in this context.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is the main curative treatment for patients with nonfavorable acute myeloid leukemia (AML); however, donor availability is a limitation for the process, and when possible, transplantation from HLA-matched related donors (MRD) is preferred. Transplantation from a 10/10 HLA–matched unrelated donor (MUD) is another valuable option, with an acceptable safety profile, and compares favorably with MRD [1-4]. In the absence of MRD or MUD, use of umbilical cord blood (UCB) as an alternative donor has emerged as a promising strategy. Indeed, because of a permissive HLA disparity [5], the outcome of UCB Allo-HSCT has been described to be similar to the results of unrelated marrow transplantation in adults; thus, adding to the initial

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Table 1
Patients' Characteristics

Characteristic	MRD/MUD (n = 49)		UCB (n = 32)		*P* Value
	n	%	n	%	
Age, median (range), yr	54	(20-69)	50	(18-66)	.032
Cytogenetics					
Favorable	5	10	3	9	
Intermediate	26	53	17	53	.992
Unfavorable	18	37	12	38	
Disease status at Allo-HSCT					
CR1	29	59	15	47	
CR > 1	13	27	13	41	.547
No CR	7	14	4	13	
Induction therapy for CR1					
1 Course	8	28	5	33	.737
2 Courses	21	72	10	67	
Conditioning regimen	Flu + Bu + ATG		Flu + Cy + TBI		
GVHD prophylaxis	CSA alone		CSA + MMF		
Stem cell source	PBSC		UCB		
Follow-up, median (range), mo	55	(28-100)	66	(30-87)	.349

Flu indicates fludarabine; Bu, busulfan; Cy, cyclophosphamide; TBI, total body irradiation; CSA, cyclosporine A; MMF, mycophenolate mofetil; PBSC, peripheral blood stem cells.
Data presented are n (%), unless otherwise indicated.

observation in children [6,7]. However, UCB Allo-HSCT in adult recipients after myeloablative regimens is associated with a graft failure rate of 8% [8] to 20% [7], slow hematological recovery, delayed immune reconstitution [9,10], high risk of viral complication [11,12], and, thus, it unfavorably compares with MRD [6,13]. More recently, the use of double UCB units and reduced-intensity conditioning (RIC) regimens reportedly supported rapid neutrophil recovery, low nonrelapse mortality (NRM), and produced similar outcomes with other graft sources [14-16]. Consequently, UCB Allo-SCT is increasingly considered as an option for high-risk AML patients who lack an MRD/MUD in a risk-adapted strategy [17,18]. Previously published studies that compared UCB with MRD or MUD [13,19-22] did not specifically focus on high-risk AML. Here, we investigated the outcome of high-risk AML patients undergoing RIC Allo-SCT from either MRD/MUD or UCB at a single transplantation program.

PATIENTS AND METHODS

Selection Criteria

Patients with high-risk AML who had undergone Allo-HSCT after RIC regimens were included in the present study. *High risk* was defined according to institutional guidelines, by the presence of at least 1 of the following criteria: (1) absence of complete remission (CR) at the time of Allo-SCT; (2) patient in second CR or more advanced CR (CR > 1), whatever the initial cytogenetic outcome; (3) adverse karyotype abnormalities based on the Medical Reseach Council cytogenetic stratification [23]; or (4) first CR achieved after more than 1 induction course [24]. In this report, we compared the outcome of selected patients who underwent transplantation using MRD or MUD (MRD/MUD) and those using UCB when such a donor was missing. Our institutional review board approved this study and all the patients gave signed informed consent in accordance with the Helsinki declaration.

UCB Group

All these patients underwent transplantation between 2005 and 2011. The UCB group received a RIC regimen containing cyclophosphamide (50 mg/kg/day during 1 day), fludarabine (Fludara [Schering AG, Lys-Les-Lannoy, France], 40 mg/m^2/day for 5 days), and 2 Gy total body irradiation [14]. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine A (started at day −3) and mycophenolate mofetil (from day −3 to day +30). No antithymocyte globulin (ATG) was given to the UCB patients. All patients received granulocyte colony–stimulating factor from day +1 to hematological recovery. Selection criteria for cord blood units were as follows: (1) a maximum of 2 mismatches were allowed on the A, B, and DR loci between the unit(s) and the recipient; (2) in patients receiving 2 units, a maximum of 2 mismatches were allowed between both cord units; and (3) minimal dose of total nucleated cells by kilogram of body weight (TNC/kg) to select the cord units was a total of 3.0^7 TNC/kg, with at least 1 unit with a minimal dose of 2.0^7 TNC/kg in case of double cord transplantation.

MRD/MUD Group

The MRD/MUD group was used as a control group. We selected all patients who underwent transplantation for high-risk AML using MRD or MUD in the same period of time, and who received a RIC regimen based on fludarabine (Fludara [Schering AG, Lys-Les-Lannoy, France], 30 mg/m^2/day for 5 days), intravenous busulfan (Busilvex [Pierre Fabre, Boulogne-Billancourt, France], 3.2 mg/kg/d during 2 days) and rabbit ATG (Thymoglobuline [Genzyme, St. Germain-en-Laye, France], 2.5 or 5 mg/kg total dose) because it represents our standard RIC regimen for Allo-HSCT using MRD or MUD [25,26]. GVHD prophylaxis consisted of cyclosporine A alone started at day −3. All patients were given peripheral blood stem cells as the graft source from either an MRD or a high-level HLA MUD (on A, B, C, DR, and DQ loci).

Endpoints and Statistical Analyses

Baseline characteristics of both MRD/MUD and UCB groups were compared using the chi-square or Fisher's test. MRD/MUD and UCB groups were compared for the following endpoints: incidence of acute GVHD and chronic GVHD [27,28], NRM rate, relapse, leukemia-free survival (LFS), and overall survival (OS). Time to events was calculated from the date of Allo-HSCT. Cumulative incidence of GVHD, NRM, and relapse were calculated using the Prentice estimate, allowing for the consideration of competing events [29,30]. The Kaplan-Meier method was used for OS and LFS analyses [31]. For univariate analyses, Gray test and log-rank test were used to identify factors influencing cumulative incidence and survival, respectively. Variables that tend to be significant ($P < .10$) in univariate analyses were included in multivariate analyses. All survival analyses were computed with the R 2.13.1 statistical software (http://www.R-project.org).

RESULTS

Patient and Transplantation Characteristics

Eighty-one consecutive patients met the selection criteria and were included for analysis. MRD (n = 36) and MUD (n = 13) were used for 49 patients (MRD/MUD group), whereas 32 patients underwent transplantation with UCB. The baseline patient characteristics are described in Table 1 and indicate no significant difference between MRD/MUD and UCB groups, except for age; UCB patients were younger. In the UCB group, 9 (28%) and 23 (72%) patients received single and double units, respectively. In the patients receiving double cord units, HLA matching was 4/6 + 4/6 (n = 18), 5/6 + 5/6 (n = 3), 4/6 + 5/6 (n = 1), and 6/6 + 6/6 (n = 1). In the patients receiving single cord blood transplantation, HLA matching was 4/6 (n = 5), 5/6 (n = 3), and

Table 2
Outcome after Allo-HSCT according to Donor Group

Outcome	MRD/MUD (n = 49) % (95% CI)	UCB (n = 32) % (95% CI)	*P* Value
Acute GVHD			
Grade II-IV	18 (7-29)	41 (23-58)	.041
Grade III-IV	8 (1-16)	25 (10-40)	.069
Chronic GVHD			
Overall	35 (21-48)	25 (10-40)	.270
Extensive	20 (9-32)	6 (0-15)	.085
Nonrelapse mortality	22 (11-34)	16 (3-28)	.529
Relapse incidence	27 (14-40)	60 (42-78)	.006
Leukemia-free survival	50 (38-67)	25 (13-45)	.029
Overall survival	56 (43-72)	34 (21-65)	.072

CI indicates confidence interval.
All estimations are given at 48 months, except acute GVHD (day 100).

6/6 (n = 1). The median total cell dose of cord units was 5.3[7] TNC/kg (range, 3.2 to 8.0).

Transplantation-related Events

Four patients (12%) experienced graft failure in the UCB group (single unit transplantation, n = 2), whereas all patients who underwent transplantation from an MRD or MUD engrafted. There was a trend for more grade III to IV acute GVHD (25% versus 8%, $P = .069$) and less extensive chronic GVHD (5% versus 20%, $P = .085$) in UCB patients than in MRD/MUD patients (Table 2). Sixteen patients (5 in the UCB group and 11 in the MRD/MUD group) died without evidence of relapse (Table 3). The cumulative incidence of NRM at 4 years was 16% versus 22% ($P = .529$) (Figure 1A) in the UCB and MRD/MUD groups, respectively, whereas that of GVHD and NRM were similar in patients receiving single versus double UCB (data not shown).

Cumulative Incidence of Relapse

Relapse occurred in 19 UCB patients and in 14 MRD/MUD patients, leading to a higher cumulative incidence of relapse at 4 years of 60% versus 27% in UCB and MRD/MUD patients, respectively ($P = .006$) (Table 2, Figure 1B). We did not find a difference between patients who received single versus double UCB (data not shown). Among patients who underwent transplantation in CR1, the 4-year relapse incidence remained significantly higher in the UCB group than in the MRD/MUD group (67% versus 24%, $P = .007$).

Survival

We observed a lower 4-year LFS in the UCB group (25%) than in the MRD/MUD group (50%) ($P = .029$) (Table 2, Figure 2A). There was a trend to a lower 4-year OS in UCB patients (34%), but it was not significantly different from that in MRD/MUD patients (56%) ($P = .072$) (Table 2, Figure 2B). After adjustment in a multivariate model, including disease status at the time of Allo-HSCT and cytogenetics, the use of UCB significantly influenced LFS (hazard ratio, 2.0; 95% confidence interval, 1.1 to 3.6; $P = .018$), and was associated with a trend for shorter OS (hazard ratio, 1.7; 95% confidence interval, .9 to 3.2; $P = .093$).

Table 3
Causes of Death in Patients Who Died at Last Follow-Up (n = 42)

Cause of Death	MRD/MUD (n = 21)	UCB (n = 21)
Deaths without evidence of relapse	11 (52)	5 (24)
GVHD-related deaths	5 (24)	3 (14)
Infection without GVHD	5 (24)	2 (10)
Other	1 (5)	0 (0)
Relapse-related deaths	10 (48)	16 (76)

Data presented are n (%).

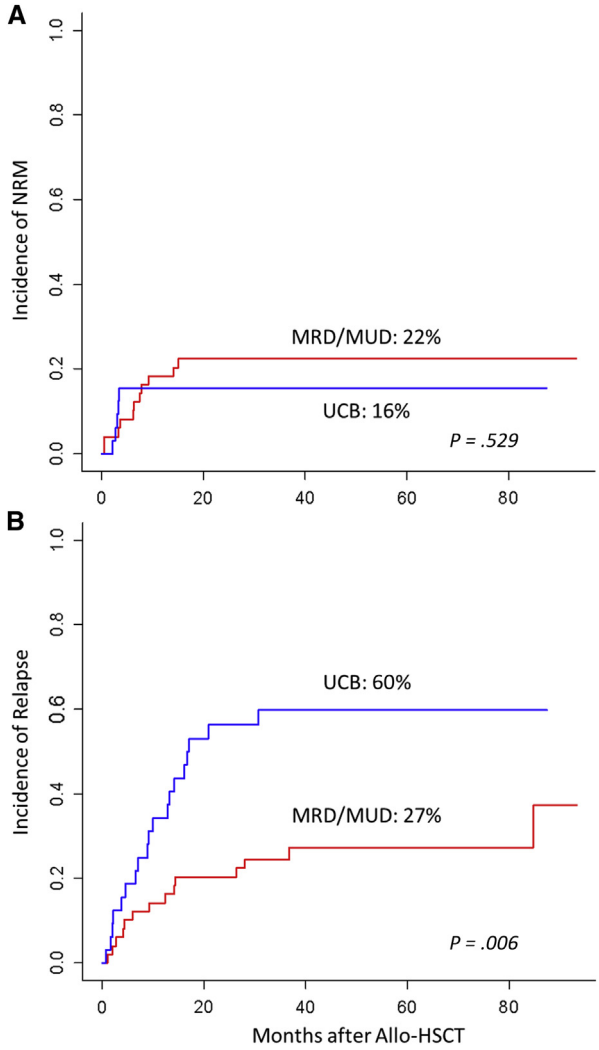

Figure 1. Cumulative incidences of NRM (A) and relapse (B) in the MRD/MUD and UCB groups.

DISCUSSION

We analyzed high-risk AML patients who underwent transplantation with UCB at a single institution and compared their outcome with patients who underwent transplantation with an MRD/MUD. To have a homogeneously treated control arm, we selected consecutive patients with high-risk AML who underwent transplantation from an MRD/MUD in the same period of time and who received a fludarabine-busulfan-ATG–based RIC regimen because it represented the standard of RIC at our institution [25]. The incidence of grade III and IV acute GVHD was higher in the UCB group (25% versus 8%), who did not receive ATG, whereas the entire MRD/MUD group did. On the contrary, incidence of extensive chronic GVHD (6%) was 3-fold lower in UCB than in MRD/MUD (20%). However, these differences of GVHD incidence could be related to both graft source and conditioning regimen, including GVHD prophylaxis disparity. Our results that present a similar NRM of about 15% to 20% in both UCB and MRD/MUD recipients suggest that RIC

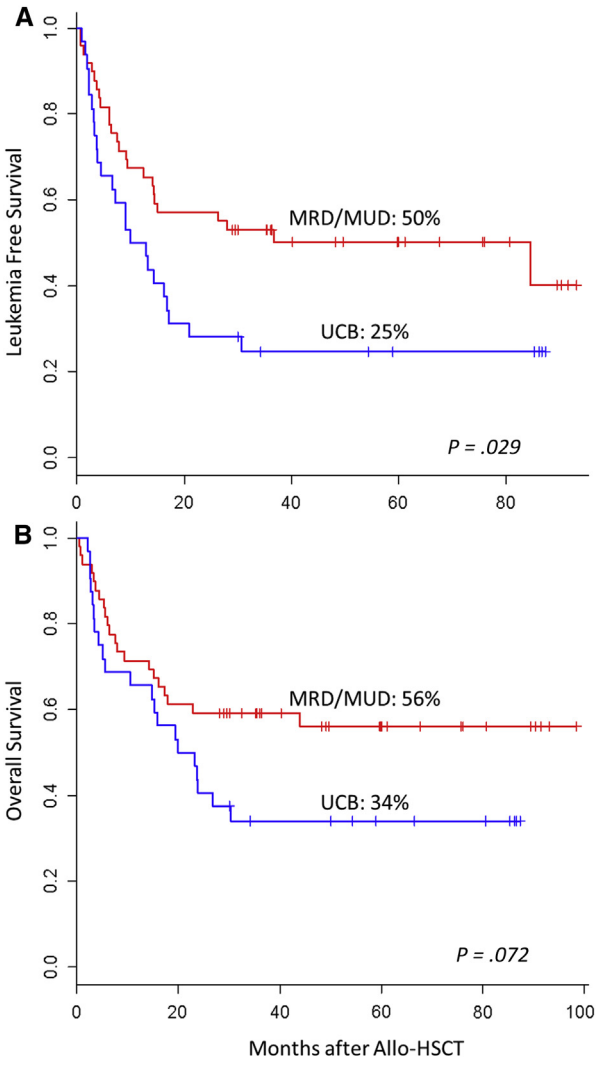

Figure 2. Leukemia-free (A) and overall survival (B) in MRD/MUD and UCB groups.

Allo-HSCT allows for extending transplantation to patients who lack an MRD or MUD, without increased transplantation-associated mortality. These results are in line with previous reports on UCB RIC Allo-HSCT [14,16,32].

Several studies have compared the efficacy of UCB Allo-HSCT and have demonstrated that the incidence of relapse is similar to MRD or MUD Allo-HSCT in different contexts of hematological diseases and/or conditioning the regimen intensity [13,22,32,33]. However, none of these studies specifically focused on high-risk AML patients who underwent transplantation after RIC regimens; in this study, we specifically evaluated the efficacy of UCB compared with MRD/MUD in patients with high-risk AML who underwent transplantation after RIC. We observed a high incidence of relapse after UCB Allo-HSCT (60%), whereas relapse occurred in 27% of MRD/MUD patients, and this observation also stands true in patients who underwent transplantation in CR1. Thus, approximately one half of the patients who underwent transplantation in this situation will relapse after UCB Allo-SCT prepared with a nonmyeloablative regimen, showing the insufficient disease control of this procedure. We suppose that the lower myeloablative potential of the conditioning regimen used in the UCB group explains, in part, the lower disease control. Indeed, we previously reported that in unselected patients who underwent transplantation from an MRD, the busulfan-based RIC resulted in better disease control than the fludarabine TBI-based nonmyeloablative conditioning regimen [34]. However, this statement should be confirmed in the setting of UCB Allo-HSCT. To better assess this issue, we reviewed a published series of UCB Allo-HSCT, including a high proportion of patients with AML who received either RIC or myeloablative conditioning (MAC) regimens (Table 4). This review confirms the high incidence of relapse, approximately 50%, in patients who underwent transplantation with UCB after a RIC regimen. Interestingly, MAC regimens seem to produce better disease control, with relapse rates ranging from 9% to 31%. However, Atsuta et al. and Sanz et al. observed a high NRM of 33% and 39%, respectively, offsetting the benefit associated with better disease control and eventually producing similar LFS (about 35%) when compared with the RIC regimen [35,36]. Oran et al. directly compared the RIC and MAC regimens in UCB Allo-HSCT for AML patients and showed a higher incidence of relapse after RIC (43% versus 9%), leading to worse LFS (31% versus 55%) [37]. These results stress how important it is to measure and optimize the conditioning intensity in various settings, defined by the nature and stage of the underlying disease for which Allo-HSCT is being used and by the stem cell source. In the context of UCB Allo-HSCT for high-risk AML patients, the optimal balance between transplantation mortality and the antileukemic effect remains to be defined. A preparative regimen with increased/intermediate myeloablative potential but acceptable toxicity deserves to be tested as an alternative to both standard MAC

Table 4
Major Series of UCB Allo-HSCT Prepared with RIC or MAC and Including High Proportion of AML Patients

Series	N*	Conditioning regimen	% AML	Acute GVHD (III-IV)	Chronic GVHD	NRM	Incidence of Relapse	LFS	OS
RIC series									
Present study	32	FLU-CY-TBI 2 Gy	100%	25%	25%	16% at 4 yr	60% at 4 yr	25% at 4 yr	34% at 4 yr
Brunstein et al. [32]	121	FLU-CY-TBI 2 Gy +/− ATG	82%	17%	34%	19% at 2 yr	49% at 2 yr	31% at 2 yr	37% at 2 yr
Majhail et al. [33]	60	FLU-CY-TBI 2 Gy +/− ATG	73%	26%	33%	25% at 2 yr	47% at 2 yr	22% at 3 yr	31% at 3 yr
Oran et al. [37]	70	FLU-CY-TBI 2 Gy +/− ATG	100%	16%	30%	19% at 2 yr	43% at 3 yr	31% at 3 yr	NA
Ponce et al. [38]	30	FLU-CY-TT-TBI 4 Gy	71%	7%	10%	28% at 2 yr	11% at 2 yr	60% at 2 yr	60% at 2 yr
MAC series									
Atsuta et al. [35]	173	Different MAC	100%	NA	28%	33% at 2 yr	31% at 2 yr	36% at 2 yr	43% at 2 yr
Oran et al. [37]	45	FLU-CY-TBI 13 Gy	100%	31%	34%	27% at 2 yr	9% at 3 yr	55% at 3 yr	NA
Sanz et al. [36]	49	TT-BU-Cy-ATG TT-BU-FLU-ATG	100%	15%	46%	39% at 2 yr	19% at 2 yr	37% at 4 yr	NA
Ooi et al. [42]	77	CY-AraC-FLU-TBI 12 Gy	100%	25%	84%	10% at 5 yr	26% at 5 yr	63% at 5 yr	NA

NA indicates not available; TT, thiotepa; AraC, cytarabine.
* Number of patients who underwent transplantation from UCB in the series.

and nonmyeloablative regimens for high-risk AML patients [38]. Alternatively, Allo-HSCT from haploidentical donors could be an interesting option. It was reported that outcomes after T cell–replete haploidentical Allo-HSCT with post-transplantation cyclophosphamide could approach those after UCB or HLA matched related or unrelated donors [39,40]. However, with no prospective comparison in the specific setting of AML, the question of the best alternative donor remains unsolved [41].

We conclude that although the use of UBC Allo-HSCT offers a therapeutic option for high-risk AML patients without an MRD or MUD, approximately one half will relapse and have a poor outcome after receiving the RIC regimen. New strategies to improve the antileukemic effect after UCB Allo-SCT are needed, including the design and evaluation of modified and improved myeloablative regimens with low mortality, as well as post-transplantation therapies. Alternatively, other types of donors, including mismatched unrelated or haploidentical donors, need consideration.

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